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Published in:
Quality & Safety in Health Care

DOI:
10.1136/qshc.2008.030106

Publication date:
2010

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Qual Saf Health Care 2010 19: 411-415 originally published online April 27, 2010
doi: 10.1136/qshc.2008.030106

Cardiometabolic treatment decisions in patients with type 2 diabetes: the role of repeated measurements and medication burden

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► A supplementary appendix is published online only. To view this file please visit the journal online (http://qshc.bmj.com).

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Accepted 3 January 2009
Published Online First 27 April 2010

ABSTRACT

Purpose Clinical guidelines for cardiometabolic risk management indicate a simple threshold-based strategy for treatment, but physicians and their patients may be reluctant to modify drug treatment after a single elevated measurement. We determined how repeated measurements of blood pressure, cholesterol and haemoglobin A1c affect general practitioners' decisions to start or intensify medication in patients with type 2 diabetes. We also evaluated whether medication burden altered these decisions.

Methods We conducted a cohort study in 3029 patients managed by 62 general practitioners (GPs). We assessed the predictive value of the last risk factor measurement, the number of successive measurements above target level and the percentage change between the last two measurements. Medication burden was assessed as the number of drugs concurrently used. Effects on treatment decisions were estimated by multilevel logistic regression analysis, correcting for clustering at GP level.

Results Repeated high levels of diastolic blood pressure increased the likelihood to start antihypertensive medication (OR=2.08, CI 1.37 to 3.17). Repeated high haemoglobin A1c levels affected intensification of oral glucose-lowering medication (OR=1.71, CI 1.44 to 2.03). Modification of lipid-lowering medication was limited, and only affected by the last total cholesterol level. Starting treatment for all three risk factors, as well as intensifying antihypertensive treatment, was more likely in patients already using more drugs for other chronic diseases.

Conclusions Waiting for the next measurement before deciding to change medication can explain in part the apparent undertreatment for hypertension and hyperglycaemia, but not for hypercholesterolaemia. Medication burden was not a barrier for treatment modification.

Adequate treatment of cardiometabolic risk factors in patients with diabetes is important.[1] Clinical guidelines describe strict target levels above which pharmacotherapy should be started or intensified. Although considerable progress has been achieved in the quality of diabetes care, undertreatment still remains a concern.[2–5]

Several reasons for undertreatment have been identified, including concerns about polypharmacy, medication adherence, intolerance and costs.[6–9] Postponing treatment intensification because of improvement already being made or competing demands are other commonly reported reasons.[9–14] Physicians may be reluctant to modify treatment after a single elevated measurement.[11 12 15 16] Especially, in patients with low overall risk, this could be the case. Furthermore, in older patients using multiple medications, a conservative approach could be motivated by fears of medication burden.[8 9 13 17]

Despite this rationale for awaiting a next observation before deciding to intervene, few studies include more than one observation moment to assess appropriate action. Studies that did include a follow-up period suggest that physicians take more than one measurement outcome into account when making treatment decisions.[12 18 19]

The objective of this study is to investigate the decisions of general practitioners (GPs) to start or intensify medication treatment in patients with type 2 diabetes and determine how repeated measurements of blood pressure, cholesterol and haemoglobin A1c (HbA1c) levels contribute to these decisions. We evaluated whether the treatment decisions are associated with the number of previous measurements above target level, with recent improvement or worsening of the risk factor, as well as with any other of the three risk factors. This will give insight in the influence of each of these factors on the decision-making process. We further tested whether medication burden affects this decision and whether the risk factors are weighed differently for patients with a high or low overall risk.

METHODS

Study population and setting

Our study population comprised 3029 patients who were managed for their diabetes by 1 of 62 GPs participating in a regional diabetes project in the northern Netherlands in 2004 and 2005. Twenty-seven per cent of the GPs were female, and the mean age was 49 years for male subjects and 43 years for female patients. Twenty-five (18%) practised alone, six (10%) in a duo practice and 31 (50%) worked in a group practice. Of the 45 general practices, 13 (29%) were located in rural areas and were allowed to dispense drugs. All their patients whom they managed themselves with a diagnosis of type 2 diabetes at the beginning of the study period were included.

In The Netherlands, nearly all inhabitants are registered with a GP, who is the gatekeeper of the healthcare system. In our study area, a regional diabetes facility offers support to GPs. Patients can be referred to this facility for physical examination and

laboratory tests. The results are reported back to the GPs who remain responsible for further treatment and treatment modifications. Diabetes patients usually visit their GP every 3 months for a check-up and medication refills. During the study period, there were no governmental or insurance restrictions on the prescription or reimbursement for the drugs included in our study.

Design and data collection

We conducted a cohort study to assess the influence of repeated risk factor measurements on the decision to modify antihypertensive, lipid-lowering and oral blood-glucose-lowering treatment. Clinical measurements, comorbidity, prescriptions and demographic data were collected from November 2001 until March 2005. All information was extracted from electronic patient record systems at the GPs' offices and the regional diabetes facility using a validated software programme.[20] All GPs in our study prescribe electronically, ensuring complete prescribing information. For research using anonymous medical records no ethics committee approval is needed in The Netherlands.[21]

Outcome measures

Treatment modification was the studied endpoint, defined as the first treatment start or intensification between October 2003 and September 2004. Patients were considered to start treatment when they received a first prescription after receiving no prescriptions for that therapeutic group during the previous 6 months (twice the duration of a standard prescription for chronic medication in The Netherlands). A modification was considered intensification when a new drug class was added or the medication dosage was increased. A switch to another drug class, that is, starting a new drug when the original medication was not continued within 120 days from the calculated end date, was not considered treatment intensification.

Patients with incomplete follow-up to assess treatment intensification and patients receiving maximal medication at baseline were excluded from the analyses. The definitions for maximal medication were derived from the Dutch Pharmacotherapy Compendium[22] and prevailing national practice guidelines for GPs and at the time of the study.[23–25] For antihypertensive treatment, three drugs from different classes prescribed at maximum maintenance dosage or more than three drugs was considered maximal medication. For lipid-lowering treatment, prescribing one drug at maximum dosage or more than one drug was considered maximal medication. For glucose-lowering treatment, insulin use was seen as maximal medication.

Predictors

As predictors of treatment modifications, we included the most recent measurements of systolic and diastolic blood pressure, total serum cholesterol, and HbA1c (called "last value") and two aspects of previous risk factor information: (1) the number of last successive measurements above target level (called "intensity") and (2) per cent change in risk factor level, that is, the relative difference between the last two measurements (called "change"). Measurements in the preceding year were included for blood pressure and HbA1c, and 2 years for total cholesterol since this was usually measured once a year. Target levels were derived from the practice guidelines at the time of our study: systolic blood pressure<140 mm Hg, diastolic blood pressure<90 mm Hg, total cholesterol<5.0 mmol/l and HbA1c<7.0%.[23–25]

Medication burden was assessed by counting unique drugs prescribed in 6 months up to the medication change, separately for risk factor specific drugs and drugs for other chronic diseases. This included all drugs at the lowest level of the Anatomical Therapeutic Chemical classification system in classes A, B, C, H, L, M, N or R.[26] Fixed combinations of drugs were counted as one drug.

Analysis

Multilevel logistic regression was used, correcting for clustering by allowing a random effect at GP level. We performed complete subject analyses, enabling us to draw conclusions on the influence of the risk factor information when available on the treatment decisions. We constructed separate predictive models for starting and intensifying treatment, adjusted for age, sex, diabetes duration, albuminuria, body mass index, coronary comorbidity (angina pectoris, myocardial infarction, heart failure, coronary artery bypass graft, coronary angioplasty, atrium fibrillation) and other diabetes-related conditions (stroke, transient ischaemic attack, peripheral arterial disease, neuropathy, amputations, retinopathy). Interaction terms between the predictors and sex/age were explored, and regression models were checked for collinearity. Overall models and models stratified on cardiovascular risk were built. Risk stratification was based on UKPDS 10-year cardiovascular risk scores (low-risk<20%, high-risk≥20%).[27]

RESULTS

The patients were aged 66 (12) years, and 56% were female. At baseline, 14% had a noted history of coronary comorbidity, and 13% suffered from other diabetes-related conditions. The median number of concurrently prescribed chronic drugs was 4. Risk factor measurements were available in 75% to 82% of the cases (table 1).

Treatment

Of the 3029 patients in our study population, 63%, 31% and 80% were using antihypertensive, lipid-lowering and glucose-lowering medication at baseline, respectively. During the study period, treatment was started for 8%, 11% and 7% of the patients untreated at baseline. Of patients treated at baseline, 16%, 0.2% and 13% were already on maximal treatment. Treatment intensifications were seen in another 15%, 5% and 30% of the patients already treated. In 49%, 66% and 73% of the cases, intensification was achieved without increasing the number of drugs.

Predictors of treatment modification

The results of the regression models are presented in figure 1, and the numerical information is available in the online appendix to this paper.

For starting antihypertensive treatment, the level of the last systolic blood pressure (p=0.001) and repeated high levels of diastolic blood pressure (p=0.001) were independent predictors. Treatment intensification was more likely when the most recent systolic (p=0.002) or diastolic blood pressure (p=0.021) measurements were higher but was not affected by previous measurements. The likelihood to start or intensify lipid-lowering medication was also only affected by the level of the last cholesterol measurement (p<0.001 and p=0.002). Starting or intensifying glucose-lowering medication was strongly associated with the level of the last HbA1c measurement (p<0.001 for both), but repeated high HbA1c levels (p<0.001) and a recent increase in HbA1c (p=0.002) also increased the likelihood of treatment intensification.

There was no significant influence of any of the other risk factor levels on the treatment decisions. In patients already

Table 1 Patient characteristics at baseline, October 2003 (n=3029)

Characteristic	Data availability (%)	Median number of measurements (IQR) during study period*	Mean (SD) or %
Age	100.0		66 (12)
Female, %	100.0		56
Diabetes duration	99.0		4 (6)†
Systolic blood pressure	81.8	4 (2)	147 (20)
Diastolic blood pressure	81.7	4 (2)	81 (10)
HbA1c	76.9	3 (2)	7.3 (1.3)
Total cholesterol	74.8	2 (3)	5.2 (1.0)
Body mass index	57.9	3.5 (1)	29.6 (5.4)
Total number of concurrent drugs	100.0		4 (4)†
Presence of coronary comorbidity, %			13.8
Presence of other related conditions, %			12.5
Albuminuria, %			8.1

*12 months for all factors except total cholesterol (24 months).
†Median (IQR).
HbA1c, Haemoglobin A1c; IQR, interquartile range.

using more drugs for other chronic diseases, starting treatment for all three risk factors ($p<0.001$) and intensification of antihypertensive treatment ($p<0.001$) was more likely. The number of risk factor specific drugs already prescribed did not influence the likelihood of treatment modification.

The stratified analyses on overall cardiovascular risk showed essentially the same predictors for starting and intensifying medication with some shifts between the strata (online appendix). Compared to the associations found in the total patient group, the association of the last value of systolic blood pressure with the start of treatment increased in the high-risk group, while in the low-risk patients, this association became non-significant. The effect of repeated diastolic blood pressure measurements showed an opposite shift, increasing in the low-risk group and loosing significance in the high-risk group. For the intensification of blood-pressure-lowering medication, the effect of the last value of diastolic blood pressure on intensification remained significant only in the low-risk stratum. The association between the last value of total cholesterol and treatment intensification of lipid-lowering medication increased in the high-risk group and decreased in the low-risk stratum.

DISCUSSION

The decision to modify cardiometabolic treatment in patients with diabetes was in part influenced by repeated elevated risk factor levels. Starting antihypertensive treatment and intensifying oral blood-glucose-lowering medication were affected by repeated measurements above target level. Surprisingly, starting treatment for any of the risk factors was more likely in patients with a higher medication burden. The found associations between predictors and outcomes, although they occurred subsequent to each other in time, are not necessarily causal.

A treatment decision based on the last measurement in combination with recent history acknowledges the intrinsic variation of physiological measurement as well as other variation.[28–30] Although it has been suggested that physicians take more than one measurement into account,[12 18 19] we could only confirm this for the start of antihypertensive treatment and the intensification of oral blood-glucose-lowering medication. One could expect that a delay in acting on elevated risk factor levels is less desirable in high-risk patients. The models stratified on overall cardiovascular risk indeed showed that the impact of repeated high levels of diastolic blood pressure on the decision to start treatment was not significant in high-risk patients. No such differences were observed for the other treatment decisions. We also did not find a significant contribution of other risk factor levels on any of the treatment decisions, suggesting overall cardiovascular risk was generally not considered. This confirms previous findings showing that treatment changes were mainly determined by elevated levels of the corresponding risk factor.[31 32]

We observed an influence of both systolic and diastolic blood pressure values on the antihypertensive treatment decisions. Despite the fact that systolic blood pressure has become more important for treatment recommendations, diastolic blood pressure appeared still relevant for the GPs in our study. The decision to start treatment was influenced by the number of previous diastolic blood pressure measurements above target level. Studies looking only at the most recent measurements may therefore have underestimated the influence of diastolic blood pressure on doctors' decision making.[9]

According to physicians, concerns about medication burden and compliance are important when deciding to prescribe drug treatment to patients using multiple drugs.[8 13] In our study, the number of concurrently used drugs was not a barrier but instead positively associated with the start of medication. Previous studies conducted in the USA showed somewhat conflicting results, where a higher number of concurrently used other drugs was either found negatively associated or not associated with treatment modifications.[9 18] This discrepancy could be explained by differences in drug reimbursement between the countries studied: In The Netherlands, there is no financial burden for the patient. Also, our study showed that in many cases, drug treatment could be intensified without adding another drug. Furthermore, adding a drug might not be a problem for patients already used to a multiple-drug scheme.[33]

In contrast to antihypertensives and glucose-lowering medication, decisions to start and intensify lipid-lowering medication were not influenced by repeated risk factor measurements. Relatively few patients received lipid-lowering medication, and intensification of such medication was uncommon. As was shown in other studies, GPs may have several reservations for prescribing lipid-lowering medication, such as expecting very few benefits in older patients or in patients with near-goal lipid levels.[34 35] Also, patients can be reluctant to take them. The results from our study show that the reluctance to prescribe lipid-lowering drugs is not affected by repeated elevated lipid levels and might be seen as a decision of the GP not to prescribe lipid-lowering medication in some of their patients.

This study has some limitations. The GPs in our study may not be representative of all GPs in The Netherlands. They participated voluntarily in a regional diabetes project, which could have resulted in a group of GPs included with a higher interest in diabetes than in general. The data used in this study come from the first retrospective data collection at these practices, and therefore alteration of the GPs' prescribing behaviour due to the participation in the regional project was not possible. The level of prescribing in our GP population was similar to other populations in The Netherlands.[31–36] It can be questioned whether the results are applicable to other countries. Although similar low rates of treatment and treatment intensification have been observed in other studies,[36–39] there may be intrinsic differences in the healthcare system that influence the motivation and rate of treatment modifications. Furthermore, there can

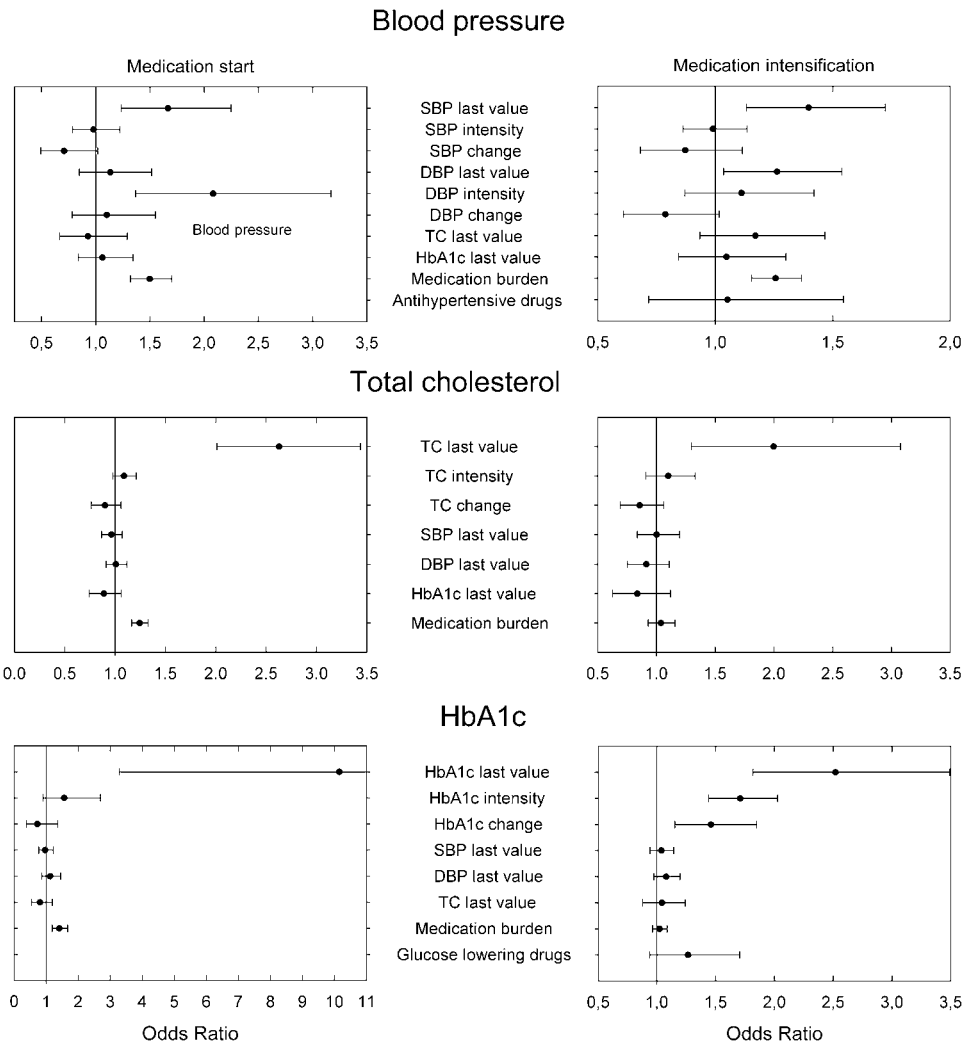

Figure 1 Predictors for starting and intensifying blood-pressure-lowering, lipid-lowering and glucose-lowering medication (adjusted odds ratio (OR) and 95% CI). Last value, the most recent measurement of the risk factor; intensity, the number of successive measurements above target level; change, the percentage change between the last two measurements; medication burden, the number of unique drugs used for other chronic diseases; antihypertensive/glucose-lowering drugs, the number of unique risk factor specific drugs used; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, haemoglobin A1c.

be unmeasured factors at the level of the GP (eg, time per consultation, GPs' workload) and the patient (eg, social economic status, educational level) that may influence the decisions.

Our reliance on data collection from medical records has both strengths and weaknesses. Incomplete registration may affect our findings. In general, prescribing data and test results are reliably documented in electronic records, but underregistration of lifestyle data is common.[40] Risk factor measurements, however, are not always routinely assessed by the GPs. In our analyses, we assume that the GPs prescribing decisions were not influenced by test results that were not noted in the medical records.

Furthermore, we were unable to correct for several potentially relevant confounders due to poor registration in the patient files, such as smoking, contraindications or patients' non-adherence or refusal of treatment, which may have resulted in an underestimation of the effect of risk factor information on the likelihood of treatment modification. One study in the UK showed that a patient's smoking status may affect the GP's decision to start lipid-lowering medication.[41] Medication adherence has been found both positively and negatively related to subsequent treatment modifications.[42–44] In a recent study, however, poor medication adherence was found to be irrelevant for the decision to intensify antihypertensive treatment.[45]

A strength of our study is that it analyses the effect of repeated risk factor measurements and concurrent medication on actual prescribing without relying on survey methods that may influence the outcomes.

This study shows that waiting for the next measurement before deciding to modify treatment can explain part of the observed undertreatment for hypertension and hyperglycaemia that has been called "clinical inertia".[15 38] The low levels of treatment modification for lipid-lowering drugs, however, cannot be explained by an awaiting attitude. Overall, cardiovascular risk seems to have some impact on the decision to start or intensify treatment. An alerting system on the combined exposure to elevated risk factors may be helpful to improve current treatment. Furthermore, quality assessment of physician performance evaluations based only on the most recent measurement of a risk factor may lead to an inaccurate view on the decision-making process.

Acknowledgements The Groningen Initiative to Analyse Type 2 Diabetes Treatment (GIANTT) group are D de Zeeuw, F M Haaijer-Ruskamp, P Denig, R O B Gans, B H R Wolffenbuttel, K van der Meer, K Hoogenberg, P Bijster, J Bolt†, L T W de Jong-van den Berg, J G W Kosterink, J L Hillege, R P Stolk, H J G Bilo.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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